REMARKS

Status of the Claims

Claims 23, 25-27, 30-34, 36, 39, 40, 42-48, 50-56 and 62-67 are pending.

Claims 23, 25-27, 30-34, 36, 39, 40, 42-48, 50-56 and 62-67 have been canceled.

Claim 67 has been objected to.

By way of this amendment, claim 67 has been amended.

Upon entry of this amendment, claims 23, 25-27, 30-34, 36, 39, 40, 42-48, 50-56 and 62-67 will be pending

Summary of the Amendment

Claim 67 has been amended to correct obvious typographical and grammatical errors.

No new matter has been added.

Claim Objections

Claim 67 has been objected to for containing informalities. Applicant has amended claim 67 to address and eliminate the informalities. Applicant respectfully requests that the objection of claim 67 be withdrawn.

Rejection under 35 U.S.C. §112, first paragraph

Claims 23, 25-27, 30-34, 36, 39, 40, 42-48, 50-56 and 62-67 have been rejected under 35 U.S.C. §112, first paragraph, because, it has been asserted, the specification, while being enabling for using the pharmaceutical compositions in isolated cells, does not reasonably provide enablement for pharmaceutical uses in animals or humans. Applicant respectfully disagrees.

It is well established that the burden of proof in an enablement rejection initially must be met by the Office, which must put forward reasoning and evidence to support the conclusion

that one skilled in the art would not be able to practice the claimed invention without undue experimentation. The Office has not met its burden.

The central reasoning provided in support of the rejection relies on the predictability of the art factor of the factors set forth in In re Wands. The Office contends that because of toxicity questions, problems associated with oral delivery of peptides, problems associated with delivering peptides to cells, and the absence of in vivo data, one skilled in the art would not accept Applicants assertion that the claimed invention is enabled.

Cianfrocca et al. is cited as disclosing toxicity problems associated with peptides. As noted in the previous reply, the data in Cianfrocca et al. actually shows a sufficient degree of success in a Phase I trial on cancer treatment using a 5 amino acid anti-angiogenic peptide drug, for the authors to conclude that the results were positive and that the drug should proceed with further clinical testing. Thus, Cianfrocca et al. supports a finding of enablement. Nothing in Cianfrocca et al supports a question of the enablement of the claimed invention. Applicants respectfully point out that the potential for toxic side effects does not render a drug unpatentable absent clinical data. The Food and Drug Administration is the administrative agency tasked with reviewing the toxicity of a drug candidate to determine whether such drug candidate is safe and effective before it can be marketed. The standard is not the same as that which is required to establish enablement and it is improper to use the FDA standard in an evaluation of patentability. The test for enablement under the patent law is whether on skilled in the art, armed with Applicant's specification, could practice the claimed invention without undue experimentation. Nothing in Cianfrocca et al. supports the conclusion that one of skilled in the art would be required to employ undue experimentation to practice the claimed invention. Nothing in Cianfrocca et al suggests that peptides are typically so toxic that there toxicity would make their suitability for use as a cancer therapeutic unpredictable. On the contrary, Cianfrocca et al clearly shows that peptides can be viable drugs. The citation of Cianfrocca et al. does not support a

conclusion that the state of the art is sufficiently unpredictable to establish that one skilled in the art would require undue experimentation to practice the invention.

The citation of Russell-Jones as evidence that one skilled in the art would not consider the claimed invention enabled is completely misplaced. There is no requirement that all drugs must be effective by all routes of delivery to be enabled. Thus, the teachings of Russell-Jones that peptide drugs administered orally are subject to proteolysis, making them less bioavailable when delivered orally has no bearing on the enablement of the claimed invention, which does not require oral delivery. In fact, claims have been amended to refer to the compositions as injectable, i.e. in a form suitable for non-oral delivery. Russell-Jones notes self-administration by non-oral routes can be difficult and traumatic but the claims do not indicate self-administration is required nor does the difficulty and trauma associated with self-administration render the invention unpredictable. Russell-Jones raised no issues in support of a finding that the claims are not enabled.

El-Andaloussi et al (Current Pharmaceutical Design. Vol. 11: 3597-3611; 2005; cited previously), is cited in the Official Action in support of the assertion that the invention is not enabled because delivery of peptide drugs to the inside of cells to exert their pharmaceutical effects is not predictable because the cell membrane prevents entry of peptides into cells. The Office asserts that the instant specification has not shown that the claimed peptides can penetrate cells, or demonstrating their specific cell-penetrating structures and/or properties. The problems disclosed in El-Andaloussi are not present in the delivery of the peptides in the present invention. The peptides specifically bind to ST receptors, which allows the peptides to specifically overcome the problems discussed in El Andaloussi et al. As noted on page 9, lines 29-31 of the specification, the peptides of the instant invention specifically bind to a receptor (ST receptor) which is present on the cell membrane that is exposed to the outside of the cell, after which the receptor and bound ligand are internalized. One skilled in the art recognizes that ST receptors

are cellular receptors and that the problems discussed in El Andaloussi are not issues in the enablement of the present invention. Applicant urges that El Andaloussi et al. does not support a finding of non enablement.

The Office cites Voskoglou-Nomiko et al (Clinical Cancer Research. Vol. 9: 4227-4239; 2003) in support of the position that *in vitro* testing for treatment of diseases such as cancer cannot be reliably correlated to successful treatments in animals or humans. It is asserted that, based upon a review of Phase II outcomes using anti-cancer compounds found to be active *in vitro,* correlating *in vitro* cell data to human clinical outcome is highly unpredictable. Applicant urges that one skilled in the art, viewing Voskoglou-Nomiko et al., would conclude that *in vitro* data, while not definitive, is useful in assessing trends. Voskoglou-Nomiko et al state on page 4237 that "[t]he work presented here argues for emphasis to be placed on *in vitro* cell lines..." In the Conclusions section of the Abstract on page 4227, Voskoglou-Nomiko et al states

> These results suggest that under the right framework and when panels are used, the in vitro cell line and human xenograft models may be useful in predicting the Phase II clinical trial performance of cancer drugs.

Applicant respectfully urges that one skilled in the art would not conclude that the claimed invention is not enabled in view of Voskoglou-Nomiko et al.

The Office urges that one skilled in the art reasonably would not and properly should not accept in vitro results as support for in vivo activity, and that to support the conclusion that the claims are enabled, some evidence correlating in vivo results to in vitro testing at the pertinent time is required. Applicant respectfully urges that it is well settled that the proper standard is whether one skilled in the art would conclude that the claimed invention could be

practiced without undue experimentation. Under such standard, the answer is yes, the claimed invention is enabled.

Applicant respectfully requests that the rejection of the claims under 35 U.S.C. §112, first paragraph, be withdrawn.

Rejection under 35 U.S.C. §103

Claim 42 has been rejected under 35 U.S.C. §103 as being unpatentable over Duflot (U.S. Patent No. 4,999,080) in view of Gluck (U.S. Patent No. 6,040,167).

Claims 23, 25-27, 30, 32-34, 42, 43, 45-48, 50-56 and 62-67 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Duflot et al (US Patent 4,499,080; 2/12/1985; cited previously), in view of Hussain et al (EP 0341661: 11/15/1989) and Trouet et al (PNAS. Vol. 79: 626-629; 1982).

Claims 23, 25-27, 30-34, 36, 39, 40, 42-48, 50-56 and 62-67 are rejected under 35 U.S.C. §103(a) as being unpatentable over Duflot et al (US Patent 4,499,080; 2/12/1985; cited previously), in view of Hussain et al (EP 0341661; 11/15/1989) and Trouet et al (PNAS. Vol. 79: 626-629; 1982), and further in view of Lee et al (US 5,183,805; 2/2/1993).

Duflot

Each of the rejections under 35 U.S.C. §103(a) relies upon Duflot as the primary reference. Applicants respectfully urge that when the disclosure of Duflot is compared to the claims by one skilled in the art, the differences between the two are great and the Duflot teaches away from the claimed invention.

Duflot teaches peptides which can be used to induce immune responses against E. coli heat stable enterotoxin but which themselves are not toxic. The purpose of Duflot is to provide an immunogenic target which can induce an immune response which is cross-reactive with the highly toxic E. coli heat stable enterotoxin. The peptides of Duflot are not only immunogenic,

but they are non-toxic. That is, unlike the highly toxic E. coli heat stable enterotoxin, the Duflot peptides are not biologically active. The non-toxicity of the Duflot peptides arises from the absence of the intramolecular disulfide bonds between cysteine residues in the peptide. Paragraphs 9 and 11 of Duflot state:

> Now Applicant company has discovered novel synthetic peptides, without intramolecular disulfide bridges, and which at the same time show remarkable relative innocousness and induce antibodies capable of establishing linkages not only with the synthetic peptidic sequence which has induced them, but quite unexpectedly and surprisingly, with pig or human natural ST enterotoxin, and by neutralising the toxicity, despite the fact that the pig or human ST enterotoxin has intramolecular disulfide bridges.
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> ***
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> It is an object of the invention to provide non-toxic synthetic peptides, stable in biological conditions and having particularly interesting properties in respect to toxic natural ST enterotoxins.

Further, in Examples III-VI, in the subheading designated "1. Nontoxicity", Duflot states:

> The non toxicity of the peptides according to the invention is in accordance with the fact that they do not have intramolecular disulfide bridges, considering that the SH groups of the cysteyl residues are protected by protective groups, stable in a biological medium. Now, it has been shown that intramolecular disulfide bridges were indispensable for biological activity of pig and human natural ST toxin (STAPLES et al. in J. Biol. Chem. 255, 4 716-4 721 (1980).

Applicants respectfully urge that the peptides of Duflot, which necessarily are free of disulfide bonds to ensure their non-toxicity, are distinguished from the peptides set forth in the instant claims. The claims expressly state that the peptides bind to ST receptor. The peptides of Duflot do not because they do not have disulfide bonds. Duflot specifically teaches to eliminate the disulfide bonds to eliminate toxicity. Those skilled in the art would not follow the teaching of Duflot to produce a peptide that binds to the ST receptor. Rather, Duflot teaches away from producing peptides that have disulfide bonds. Thus, Duflot teaches producing peptide that are necessarily free of disulfide bonds and therefore do not bind to the ST receptor.

Attached hereto is a published abstract (Giannella RA.: Escherichia coli heat-stable enterotoxins, guanylins, and their receptors: what are they and what do they do?, J Lab Clin Med. 1995 Feb; 125(2):173-81 (Abstract).) which states:

> All these peptides have a tertiary structure,
> maintained by disulfide bridges, which is required
> for receptor occupancy and biologic activity.

The disulfide bonds are required for binding. Thus, the Duflot peptides by design would not bind to ST receptors.

The Examiner indicates that the claimed subject matter is the same as the peptides disclosed in Duflot and that the Duflot peptides "inherently possess the property of binding to ST receptors" since the peptides in the instant application and Duflot are structurally the same. While two peptides may have the same amino acid sequence, they do not necessarily inherently possess the same property. In the instant application, the peptides have a different tertiary structure. The claims recite the functional difference that arises out of the structural differences. That is, the claims recite that the peptides bind to ST receptors. The peptides of Duflot do not bind to ST receptors. The peptides of Duflot were intentionally designed to lack the tertiary structure which results in the binding and biological activity of the native peptides. One skilled in the art would not be motivated to produce peptide similar to those disclosed in Duflot that

binds to ST receptors.

Duflot and Gluck

Claims 42 has been rejected under 35 U.S.C. §103 as being unpatentable over Duflot (U.S. Patent No. 4,999,080) in view of Gluck (U.S. Patent No. 6,040,167).

Duflot, as discussed above, discloses vaccines comprising a conjugated peptide that comprises non-toxic heat stable enterotoxin peptide linked to non-toxic carrier protein. The non-toxic heat stable enterotoxin peptide has no disulfide bonds between internal cysteine residues, and accordingly, does not have the tertiary structure required to bind to ST receptors.

Gluck discloses liposomes.

It is asserted that it would have been obvious to combine the vaccines of Duflot with the liposomes of Gluck. Applicant respectfully disagrees.

Claim 42 requires that peptides that bind to ST receptors and activate guanylyl cyclase C. Duflot teaches the production of peptide which will not bind to and activate guanylyl cyclase C. Accordingly, Duflot teaches away from the claimed invention. Gluck does not rectify this teaching. Noting in the combination of Duflot and Gluck would lead one skilled in the art to produce peptides with the toxic activity and include them in a composition with liposomes. The claimed invention is not prima facie obvious in view of the combination of Duflot and Gluck

Applicant respectfully requests that the rejection of claim 42 under 35 U.S.C. §103 as being unpatentable over Duflot in view of Gluck be withdrawn.

Duflot, Hussain and Trouet

Claims 23, 25-27, 30, 32-34, 42, 43, 45-48, 50-56 and 62-67 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Duflot et al (US Patent 4,499,080; 2/12/1985; cited previously), in view of Hussain et al (EP 0341661: 11/15/1989) and Trouet et al (PNAS. Vol. 79: 626-629; 1982).

Duflot is discussed above.

Hussain discloses conjugation of non-peptides to peptides to stabilize and improve delivery of peptides through the mucosae.

Trouet discloses conjugating non-peptide drugs to peptides to carry and target anti-tumor drugs.

It is asserted that it would have been prima facie obvious to one skilled in the art to make the claimed compositions. It is asserted that one skilled in the art would use a peptide taught in Duflot as a carrier peptide to delivery therapeutic agents such as those taught in Hussain or Trouet. It is asserted that all the references teach pharmaceutical compositions comprising a carrier peptide (or protein) with an active or therapeutic agent for effective drug delivery, so it would have been obvious to one skilled in the art to substitute one agent or one peptide for the other to achieve the predictable result of making a pharmaceutical composition. Applicant respectfully disagrees.

As discussed above, Duflot teaches away from the claimed invention. Duflot teaches producing peptides which do not bind to ST receptors. Specifically, Duflot requires that the ST peptide be free of the intramolecular disulfide bonds required for the molecule's tertiary structure and activity. This is a critical requirement of the invention in Duflot. The instant claims 23 and 42, and the claims dependent there from, specifically require that the peptides which bind to ST do not active GCC, i.e. they are non-toxic. Accordingly, Duflot teaches away from the claimed invention. Furthermore, Duflot specifically teaches inactivating the toxicity of the carrier molecule. A feature of the claimed invention is that the molecule delivered with the ST binding molecule is a therapeutic agent. Duflot specifically teaches inactivating the activity of the toxic carrier peptide. Duflot specifically teaches away from the claimed invention.

Hussain et al is cited as teaching that addition of a non-peptide carrier molecule to the ST peptide of Duflot. It is asserted that one skilled in the art would do so because Hussain teaches that the addition of the non-peptide carrier improves bioavailability. Hussain et al is

directed to absorption enhancers for improving uptake of drugs delivered into mucosal tissue. The claims have been amended to each include the subject matter of one of claims 41, 57 and 58, i.e. that the pharmaceutical composition is an injectable pharmaceutical composition. As such, in addition to claims 41, 57 and 58, Hussain et al. teaches away from each of the pending claims. Specifically, Hussain et al teaches making compounds more amenable to absorption based, non-injection routes of administration. One skilled in the art would not use an absorption enhancer taught by Hussain et al. to modify Duflot in the preparation of an injectable pharmaceutical compositions. Hussain et al. teaches away from combining with Duflot and teaches away from the claimed invention.

Trouet et al. is cited as teaching the conjugation of non-peptide drugs to peptides in order to provide selective targeting of anti-tumor drugs. Trouet et al. discloses linking a known anti-tumor drug to a molecule which selectively binds to another molecule on a tumor cell in order to deliver the anti-tumor drugs to tumor cells. One skilled in the art would not use the tumor targeting taught by Trouet et al. to modify Duflot in the preparation of injectable pharmaceutical compositions of the claimed invention. Duflot teaches away from the claimed invention and one skilled in the art would not modify Duflot in direct contradiction to Duflot to achieve a result completely different from Duflot. Duflot teaches non-toxic, non-binding peptides to be used as vaccines. One skilled in the art would not disregard the teachings of Duflot/

The claims are not obvious in view of Duflot et in view of Hussain et al and Trouet et al. Applicant respectfully requests that the rejection of the claims under 35 U.S.C. §103(a) as being unpatentable over Duflot et in view of Hussain et al and Trouet et al. be withdrawn.

Duflot and Others

Claims 23, 25-27, 30-34, 36, 38-48, 50-58 and 62-66 are rejected under 35 U.S.C. §103(a) as being unpatentable over Duflot et al (US Patent 4,499,080; 2/12/1985; cited

previously), in view of Hussain et al (EP 0341661; 11/15/1989) and Trouet et al (PNAS. Vol. 79: 626-629; 1982), as applied to claims 23, 25-27, 30, 32-34, 38, 41-43, 45-48, 50-58 and 62-66 above, and further in view of Lee et al (US 5,183,805; 2/2/1993).

Duflot, Hussain et al. and Trouet et al. are each discussed above.

Lee et al. discloses conjugating non-peptide drugs including 5-fluorouracil to peptides for cancer therapeutics.

As noted above, Duflot and Hussain et al. teach away from the claimed invention and Trouet et al. requires the information in Applicant's specification in order to provide any benefit to be recognized by one skilled in the art in combining Trouet as suggested.

Applicant respectfully urges that Lee et al. also requires the information in Applicant's specification in order to establish a prima facie case of obviousness and such use is impermissible. Applicant respectfully urges that only through the use of Applicant's teaching would there be any benefit to be recognized by one skilled in the art for producing an injectable composition which includes ST receptor binding antibodies, fragments thereof or peptides which bind to ST receptors and therapeutic agents.

The claims are not obvious in view of Duflot et in view of Hussain et al and Trouet et al. and further in view of Lee et al. Applicant respectfully requests that the rejection of the claims under 35 U.S.C. §103(a) as being unpatentable over Duflot et in view of Hussain et al and Trouet et al. and Lee et al. be withdrawn.

Double Patenting Rejection

Claims 23, 25-28, 33, 34, 38 and 40 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 5 and 6 of U.S. Patent No. 5,962,220.

Claims 23, 25-28, 33, 34, 38 and 40 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, 7-10 and 13 of U.S. Patent No. 6,087,109.

Claims 23 and 28 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-24, 26, 28, 29 and 33-41 of U.S. Patent No. 7,097,839.

Claims 23, 25-28, 33, 34, 38, 40, 41, 42, 45 and 47 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 5, 10 and 12 of U.S. Patent No. 5,962,220 in view of Gluck.

As noted in previous responses, once claims have been indicated to be allowable, Applicant shall promptly provide Terminal Disclaimer as appropriate. To that end, the Examiner is invited to contact Applicant's undersigned representative and inform him of the allowability of the claims so that a Terminal Disclaimer can be promptly filed.

Provisional Double Patenting Rejection

Claims 23, 25-27, 48, 50, 51, 52, 54 and 55 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 10, 12 and 15-17 and 20-22 of copending Application No. 11/494,901 (US 20060269477). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claimed invention in the '901 application reads on the instant claimed invention.

This rejection is provisional. As the co-pending application has not yet issued, no action is required at this time.

Conclusion

Claims 23, 25-27, 30-34, 36, 39, 40, 42-48, 50-56 and 62-67 are in condition for allowance. A notice of allowability is earnestly requested. Applicant's undersigned representative hereby requests that the Examiner contact him at 610-640-7855 to discuss any unresolved issues and to arrange for the timely filing of any terminal disclaimers upon an indication of allowability of the claims.

The Commissioner is hereby authorized to charge any debit or credit any overpayment to Deposit Account No. 50-0436.

Respectfully submitted,

/Mark DeLuca, Reg. #33,229/
Mark DeLuca
Registration No. 33,229

Dated: January 26, 2009
Pepper Hamilton LLP
400 Berwyn Park
899 Cassatt Road
Berwyn, PA 19312-1183
Tel: 610.640.7855
Fax: 610.640.7835

Attachment: Giannella RA.: Escherichia coli heat-stable enterotoxins, guanylins, and their receptors: what are they and what do they do?, J Lab Clin Med. 1995 Feb; 125(2):173-81 (Abstract).